Pestic. Sci. 1998, **53**, 186–192

Miticidal Pyrethroids Having an Isobutyranilidoxime Ether Skeleton

Keiichiro Nishimura,[1] Zhi-Ming Cheng,[2]* Yoshihiro Minamite[3] & Toshio Fujita[2]‡

[1] Research Institute for Advanced Science and Technology, Osaka Prefecture University, Sakai, Osaka 599-8570, Japan
[2] Department of Agricultural Chemistry, Kyoto University, Kyoto 606-8224, Japan
[3] Central Research Laboratories, Dainippon Jochugiku Company, Ltd, Toyonaka, Osaka 561-0827, Japan

(Received 17 December 1997; accepted 9 February 1998)

Abstract: Isobutyranilidoxime *meta*-phenoxybenzyl ethers and related compounds were synthesized. Their insecticidal activities measured against *Periplaneta americana* by injection were lower than that of phenothrin by factors of at least 1/60. However, some compounds were comparable to or only slightly less potent than phenothrin and tetramethrin in miticidal activity tested by a contact method against *Dermatophagoides farinae*, *D. pteronyssinus* and *Tyrophagus putrescentiae*. © 1998 SCI

Pestic. Sci., **53**, 186–192 (1998)

Key words: pyrethroids; phenothrin; tetramethrin; isobutyranilidoxime *meta*-phenoxybenzyl ethers; insecticide; miticide

1 INTRODUCTION

The structure of pyrethrins has been extensively modified to obtain novel classes of pyrethroid insecticides. One of the major modification directions gives compounds that are stable in the insect body against metabolic detoxication and sufficiently stable, but not too persistent in the environment against (bio)degradation. These compounds include phenothrin,[1] fenvalerate,[2] etofenprox,[3] silafluofen,[4] and many others developed for the control of agricultural pest insects.[5,6] Their hydrophobicity appears to be higher than that of allethrin, which is the first synthetic pyrethroid used against such sanitary pests as flies and mosquitoes. Some of above hydrophobic pyrethroids of non-ester type have low fish toxicity and are used against paddy-field pest insects.[3,4] Another direction is to introduce a hydrophilic moiety to give compounds less hydrophobic than allethrin, including imidomethylol esters,[7–9] amidines[10] and oxime ethers.[11] Other structural modifications in this direction are also feasible, because the optimum hydrophobicity varies depending on the route of administration as well as the type of biological effect.[12,13]

In this study, we set out to prepare a new class of pyrethroids having a hydrophilic sub-structure such as an amidoxime ether, which had been suggested by a database-aided software system, EMIL,[14] which releases candidate structures depending upon an input lead structure.[15,16] We report here compounds having one of the candidate structures that are not insecticidal but are miticidal against some house-dust mite species.

2 MATERIALS AND METHODS

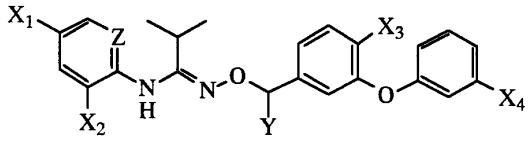
2.1 Compounds

Piperonyl butoxide, an inhibitor of oxidative metabolism, was a commercially obtained reagent-grade sample. Tetramethrin and phenothrin were the samples as reported previously.[17,18] Other compounds listed in Table 1 were prepared as described below. General structures and the synthetic route are shown in Fig. 1.

* To whom correspondence should be addressed at: Shanghai Pesticide Research Institute, Xie Tu Road, Shanghai 200032, China.
Email address: nishi@riast.osakafu-u.ac.jp
‡ Present address: EMIL Project, 305 Kyogosho, 492 Umeyacho, Kyoto 604-8057, Japan.

 Pestic. Sci. 0031-613X/98/$17.50. Printed in Great Britain

TABLE 1
Insecticidal and Miticidal Activities of Test Compounds



	Compounds						*Insecticidal*		*Miticidal (%)*[a]		
No.	X_1	X_2	X_3	X_4	*Y*	*Z*	*MLD (mol)*	*Relative*	D.f.[b]	D.p.[c]	T.p.[d]
IV-1	C_2H_5O	H	H	H	H	CH	$6{\cdot}2 \times 10^{-8}$	0·31	68	37	25
IV-2	C_2H_5O	H	H	H	Me	CH	$3{\cdot}6 \times 10^{-7}$	0·05	0	3	13
IV-3	C_2H_5O	H	H	CH_3O	H	CH	$2{\cdot}2 \times 10^{-7}$	0·09	3	5	34
IV-4	C_2H_5O	H	F	H	H	CH	$2{\cdot}0 \times 10^{-8}$	0·95	3	12	8
IV-5	Cl	H	H	H	H	CH	$1{\cdot}1 \times 10^{-7}$	0·17	36[e]	17[e]	7[e]
IV-6	Cl	H	H	CH_3O	H	CH	$3{\cdot}6 \times 10^{-7}$	0·05	9	43	—[f]
IV-7	CF_3	Cl	H	H	H	CH	$1{\cdot}2 \times 10^{-7}$	0·16	4	14	10
IV-8	CF_3	Cl	H	H	Me	CH	$1{\cdot}3 \times 10^{-7}$	0·15	74	63	29
IV-9	CF_3	Cl	H	H	H	N	$1{\cdot}5 \times 10^{-7}$	0·13	4	14	10
Phenothrin							$3{\cdot}2 \times 10^{-10}$	60	64 (±12)[g]	33 (±10)[g]	50 (±15)[g]
Tetramethrin							$1{\cdot}9 \times 10^{-8}$	1	40 (±10)[g]	18 (±6)[g]	37 (±11)[g]

[a] Percentage of the mites killed by the dose as 5 g litre^{-1} solution in acetone, unless otherwise noted.
[b] *Dermatophagoides farinae* (American house-dust mite).
[c] *Dermatophagoides pteronyssinus* (European house-dust mite).
[d] *Tyrophagus putrescentiae* (mold mite).
[e] With 10 g litre^{-1} solution in acetone.
[f] Not measured.
[g] Standard deviation for three runs.

Yields were not optimized. Compound structures were confirmed by NMR spectroscopy in deuterochloroform. The final products (compounds **IV** in Fig. 1) were also confirmed by elementary analyses for C, H and N. The results are listed in Table 2.

2.1.1 N-*Aryloxyphthalimides*[19]

2.1.1.1 N-(*3-Phenoxybenzyloxy*)*phthalimide* (***II-1***). To a solution of *N*-hydroxyphthalimide (3·00 g, 18·4 mmol) and potassium carbonate (1·93 g, 14·0 mmol) in dimethyl sulfoxide (DMSO, 20 ml), 3-phenoxybenzyl chloride (8·00 g, 36·6 mmol), which was prepared from 3-phenoxybenzyl alcohol and thionyl chloride, was added dropwise at a temperature lower than 30°C under stirring. The solution was further stirred at room temperature for 24 h, then poured over ice-water (60 ml) and the solid formed collected by filtration. The product was recrystallized from ethanol. Yield 4·94 g

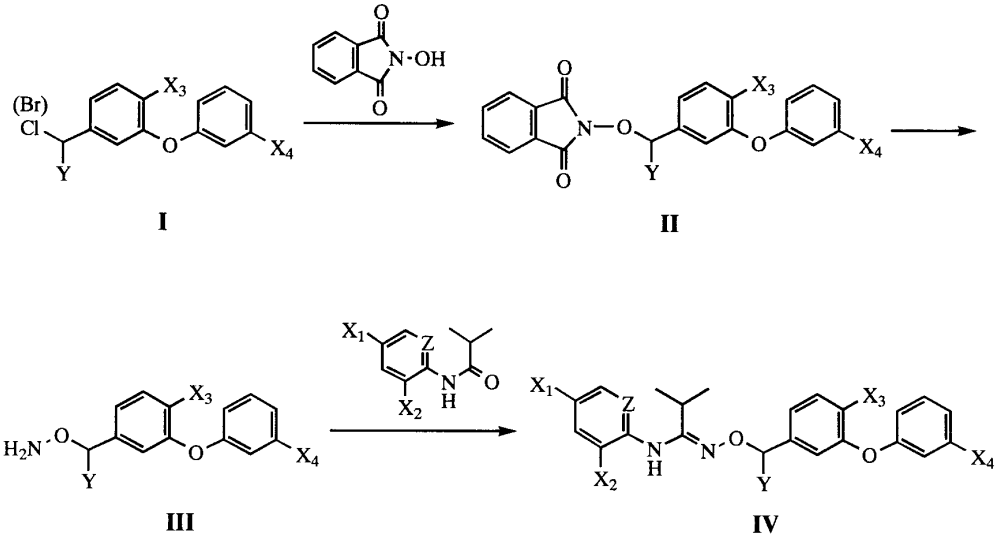


Fig. 1. Synthetic scheme for compounds listed in Table 1.

TABLE 2
Elementary Analyses of the Final Compounds

		C (%)		*H* (%)		*N* (%)	
No.	*Formula*	*Calcd*	*Found*	*Calcd*	*Found*	*Calcd*	*Found*
IV-1	$C_{25}H_{28}N_2O_3$	74·22	73·95	6·99	6·75	6·93	6·85
IV-2	$C_{26}H_{30}N_2O_3$	74·60	74·61	7·24	7·14	6·69	6·75
IV-3	$C_{26}H_{30}N_2O_4$	67·10	66·98	6·16	6·25	6·10	6·12
IV-4	$C_{25}H_{27}FN_2O_3$	73·85	74·06	6·97	7·26	6·45	6·74
IV-5	$C_{23}H_{23}ClN_2O_2$	69·94	69·66	5·88	5·82	7·09	6·98
IV-6	$C_{24}H_{25}ClN_2O_3$	67·83	67·60	5·94	5·92	6·59	6·69
IV-7	$C_{24}H_{22}ClF_3N_2O_2$	62·26	62·53	4·80	4·78	6·05	6·01
IV-8	$C_{25}H_{24}ClF_3N_2O_2$	61·95	62·03	5·08	5·09	5·85	5·87
IV-9	$C_{23}H_{21}ClF_3N_3O_2$	62·82	63·02	4·61	4·59	8·11	8·11

(78%), m.p. 97–98°C. [^{1}H]NMR δ ppm: 5·13 (2H, s, CH_2), 6·81–7·81 (13H, m, aromatic).

2.1.1.2 N-(α-*Methyl-3-phenoxybenzyloxy*)*phthalimide* (***II-2***). The title compound was prepared from *N*-hydroxyphthalimide (4·89 g, 30·0 mmol), potassium carbonate (3·14 g, 22·7 mmol), and α-methyl-3-phenoxybenzyl chloride (10·5 g, 45·1 mmol), which was prepared from α-methyl-3-phenoxybenzyl alcohol, according to the method similar to that for compound **II-1**. Yield 6·96 g (66%), m.p. 93–94°C. [^{1}H]NMR δ ppm: 1·70 (3H, d, $J = 7$ Hz, $CHCH_3$), 5·43 (1H, q, $J = 7$ Hz, $CHCH_3$), 6·79–7·76 (13H, m, aromatic).

2.1.1.3 N-[*3-*(*3-Methoxyphenoxy*)*benzyloxy*]*phthalimide* (***II-3***). 3-(3-Methoxyphenoxy)benzyl bromide (3·00 g, 10·2 mmol), which was prepared from 3-(3-methoxyphenoxy)toluene and *N*-bromosuccinimide (NBS), and triethylamine (2·07 g, 20·5 mmol) were added dropwise to a solution of *N*-hydroxyphthalimide (1·67 g, 10·2 mmol) in *N*,*N*-dimethylformamide (DMF; 10 ml) under stirring. The solution was further stirred at 90°C for 5 h. After cooling, the reaction mixture was diluted with water and extracted from chloroform. The organic layer was washed with sodium hydroxide (0·2 M) solution and water, consecutively, and was dried over sodium sulfate. The residue obtained by evaporation was dissolved in isopropanol and kept in a refrigerator. The solid formed was collected and recrystallized from a mixture of benzene and hexane. Yield 1·09 g (28%), m.p. 120–121°C. [^{1}H]NMR δ ppm: 3·74 (3H, s, CH_3), 5·13 (2H, s, CH_2), 6·50–7·80 (12H, m, aromatic).

2.1.1.4 N-(*4-Fluoro-3-phenoxybenzyloxy*)*phthalimide* (***II-4***). The title compound was prepared from *N*-hydroxyphthalimide (2·72 g, 16·7 mmol), potassium carbonate (1·75 g, 12·7 mmol) and 4-fluoro-3-phenoxybenzyl bromide (7·00 g, 26·7 mmol), which was prepared from 4-fluoro-3-phenoxytoluene and NBS, according to a method similar to that for compound **II-1**. Yield 4·37 g (76%), m.p. 103–104°C. [^{1}H]NMR δ ppm: 5·07 (2H, s, CH_2), 6·80–7·84 (12H, m, aromatic).

2.1.2 Substituted benzyloxyamines[19]

2.1.2.1 3-Phenoxybenzyloxyamine (***III-1***). To a solution of **II-1** (8·00 g, 23·2 mmol) in DMF (30 ml), hydrazine monohydrate (2·32 g, 46·4 mmol) was added at 70°C and stirred for 1·5 h. After cooling, the reaction mixture was diluted with water (70 ml), acidified and filtered. Under basic conditions with sodium hydroxide (2 M), the filtrate was extracted with ether. After treatment with sodium sulfate, evaporation of the ethereal solution gave an oil. The residue was purified by column chromatography over silica gel using chloroform as an eluent, giving an oil. Yield 3·68 g (74%). [^{1}H]NMR δ ppm: 4·62 (2H, s, CH_2), 4·93 (2H, s, NH_2), 6·78–7·48 (9H, m, aromatic).

2.1.2.2 α-*Methyl-3-phenoxybenzyloxyamine* (***III-2***). To a solution of **II-2** (3·12 g, 8·93 mmol) in ethanol (65 ml), hydrazine monohydrate (0·48 g, 9·56 mmol) was added and refluxed for 2 h. After cooling, another portion of hydrazine monohydrate was added and the mixture was refluxed for 3 h. After acidification with concentrated hydrochloric acid, the reaction mixture was filtered. The filtrate was concentrated, made basic with aqueous sodium hydroxide solution and extracted with ether. After treatment with sodium sulfate, evaporation of the ethereal solution gave an oil. Yield 1·95 g (95%). [^{1}H]NMR δ ppm: 1·37 (3H, d, $J = 7$ Hz, $CHCH_3$), 4·59 (1H, q, $J = 7$ Hz, $CHCH_3$), 5·00 (2H, s, NH_2), 6·73–7·49 (9H, m, aromatic).

2.1.2.3 3-(*3-Methoxyphenoxy*)*benzyloxyamine* (***III-3***). The title compound was yielded as an oil from compound **II-3** (2·11 g, 5·62 mmol) and hydrazine monohydrate (0·56 g, 11·3 mmol) according to a method similar to that for compound **III-1**. 1·05 g, 76% yield. [^{1}H]NMR δ ppm: 3·76 (3H, s, CH_3), 4·64 (2H, s, CH_2), 4·90 (2H, s, NH_2), 6·43–7·33 (8H, m, aromatic).

2.1.2.4 4-Fluoro-3-phenoxybenzyloxyamine (***III-4***). The title compound was yielded as an oil from compound **II-4** (4·37 g, 12·7 mmol) and hydrazine monohydrate

(1·20 g, 24·0 mmol) according to a method similar to that for compound **III-1**. Yield 1·86 g (68%). [^{1}H]NMR δ ppm: 4·56 (2H, s, CH_2), 5·04 (2H, s, NH_2), 6·84–7·50 (8H, m, aromatic).

2.1.3 N-*Aryl*-N′-(*substituted benzyloxy*)*isobutyramidines*[20]

2.1.3.1 N-(*4-Ethoxyphenyl*)-N′-(*3-phenoxybenzyloxy*)-*isobutyramidine* (***IV-1***). To a solution of phosphorus pentachloride (0·67 g, 3·21 mmol) in dried chloroform (10 ml), *N*-(4-ethoxyphenyl)isobutyramide (0·58 g, 2·80 mmol), which was prepared from isobutyryl chloride and 4-ethoxyaniline, was added. The reaction mixture was refluxed for 3 h under nitrogen. After cooling, **III-1** (0·60 g, 2·80 mmol) was added and the reaction mixture was refluxed overnight under nitrogen. After cooling, an ethanolic solution of sodium ethoxide (11·2 mmol) was added and the solution was diluted with water and extracted with benzene. The benzene layer was washed with saturated sodium chloride solution and treated with sodium sulfate. The residue obtained by evaporation was purified by column chromatography over silica gel using hexane + chloroform (1 + 3 by volume) as eluent to give the title compound as a syrup. Yield 0·45 g (40%). [^{1}H]NMR δ ppm: 1·03 (6H, d, $J = 7$ Hz, $CH(CH_3)_2$), 1·40 (3H, t, $J = 7$ Hz, CH_2CH_3), 2·59 (1H, m, $J = 7$ Hz), $CH(CH_3)_2$), 3·99 (2H, q, $J = 7$ Hz, CH_2CH_3), 4·98 (2H, s, $NOCH_2$), 6·67–7·36 (13H, m, aromatic).

2.1.3.2 N-(*4-Ethoxyphenyl*)-N′-(*α-methyl-3-phenoxy-benzyloxy*)*isobutyramidine* (***IV-2***). The title compound was prepared from *N*-(4-ethoxyphenyl)isobutyramide (0·82 g, 3·96 mmol, as used for the preparation of compound **IV-1**) and compound **III-2** (0·90 g, 3·95 mmol) according to a method similar to that for compound **IV-1**. The crude product was extracted with ether. The residue obtained by evaporation was purified by column chromatography over silica gel using hexane + ethyl acetate (20 + 1 by volume) as eluent, giving a syrup. Yield 0·41 g (25%). [^{1}H]NMR δ ppm: 1·00 (6H, dd, $J = 7$ Hz, $CH(CH_3)_2$), 1·54 (3H, d, $J = 7$ Hz, $CHCH_3$), 2·56 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 4·00 (2H, q, $J = 7$ Hz, CH_2CH_3), 5·13 (1H, q, $J = 7$ Hz, $CHCH_3$), 6·77–7·36 (13H, m, aromatic).

2.1.3.3 N-(*4-Ethoxyphenyl*)-N′-[*3-*(*3-methoxyphenoxy*)-*benzyloxy*]*isobutyramidine* (***IV-3***). The title compound was prepared from *N*-(4-ethoxyphenyl)isobutyramide (0·59 g, 2·85 mmol, as used for the preparation of compound **IV-1**) and compound **III-3** (0·70 g, 2·86 mmol) according to a method similar to that for compound **IV-1**. The crude product was extracted with chloroform. The residue obtained by evaporation was purified by column chromatography over silica gel using chloroform as eluent, giving a syrup. Yield 0·40 g (32%). [^{1}H]NMR δ ppm: 1·05 (6H, d, $J = 7$ Hz, $CH(CH_3)_2$), 1·40 (3H, t, $J = 7$ Hz, CH_2CH_3), 2·53 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 3·76 (3H, s, OCH_3), 4·02 (2H, q, $J = 7$ Hz, CH_2CH_3), 5·00 (2H, s, $NOCH_2$), 6·43–7·33 (12H, m, aromatic).

2.1.3.4 N-(*4-Ethoxyphenyl*)-N′-(*4-fluoro-3-phenoxy-benzyloxy*)*isobutyramidine* (***IV-4***). The title compound was prepared from *N*-(4-ethoxyphenyl)isobutyramide (0·80 g, 3·86 mmol, as used for the preparation of compound **IV-1**) and compound **III-4** (0·90 g, 4·20 mmol) as a syrup according to a method similar to that for compound **IV-2**. A mixture of benzene and hexane was used as eluent for the column chromatography. Yield 0·88 g (52%). [^{1}H]NMR δ ppm: 1·00 (6H, d, $J = 7$ Hz, $CH(CH_3)_2$), 1·40 (3H, t, $J = 7$ Hz, CH_2CH_3), 2·47 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 3·98 (2H, q, $J = 7$ Hz, CH_2CH_3), 4·91 (2H, s, $NOCH_2$), 6·65–7·35 (12H, m, aromatic).

2.1.3.5 N-(*4-Chlorophenyl*)-N′-(*3-phenoxybenzyloxy*)-*isobutyramidine* (***IV-5***). The title compound was prepared from *N*-(4-chlorophenyl)isobutyramide (0·92 g, 4·65 mmol), which was prepared from isobutyryl chloride and 4-chloroaniline, and **III-1** (1·00 g, 4·65 mmol) as a syrup according to a method similar to that for compound **IV-3**. Yield 0·49 g (25%). [^{1}H]NMR δ ppm: 1·06 (6H, d, $J = 7$, $CH(CH_3)_2$), 2·60 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 5·00 (2H, s, CH_2), 6·78–7·46 (13H, m, aromatic).

2.1.3.6 N-(*4-Chlorophenyl*)-N′-[*3-*(*3-methoxyphenoxy*)-*benzyloxy*]*isobutyramidine* (***IV-6***). The title compound was prepared from *N*-(4-chlorophenyl)isobutyramide (0·60 g, 3·04 mmol, as used for the preparation of **IV-5**) and compound **III-3** (0·75 g, 3·06 mmol) as a syrup according to a method similar to that for compound **IV-2**. Yield 0·30 g (22%). [^{1}H]NMR δ ppm: 1·06 (6H, d, $J = 7$ Hz, $CH(CH_3)_2$), 2·71 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 3·76 (3H, s, OCH_3), 5·01 (2H, s, CH_2), 6·46–7·36 (12H, m, aromatic).

2.1.3.7 N-(*2-Chloro-4-trifluoromethylphenyl*)-N′-(*3-phenoxybenzyloxy*)*isobutyramidine* (***IV-7***). The title compound was prepared from *N*-(2-chloro-4-trifluoromethylphenyl)isobutyramide (0·79 g, 2·98 mmol), which was prepared from isobutyryl chloride and 2-chloro-4-trifluoromethylaniline, and **III-1** (0·64 g, 2·91 mmol) as a syrup according to a method similar to that for compound **IV-3**. Yield 0·32 g (23%). [^{1}H]NMR δ ppm: 1·16 (6H, dd, $J = 7$ Hz, $CH(CH_3)_2$), 2·76 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 5·02 (2H, s, CH_2), 6·84–7·66 (12H, m, aromatic).

2.1.3.8 N-(*2-Chloro-4-trifluoromethylphenyl*)-N′-(*α-methyl-3-phenoxybenzyloxy*)*isobutyramidine* (***IV-8***). The title compound was prepared from *N*-(2-chloro-4-trifluoromethylphenyl)isobutyramide (1·05 g, 3·95 mmol, as used for the preparation of compound **IV-7**) and compound **III-2** (0·90 g, 3·93 mmol) as a syrup according to a method similar to that for compound **IV-1**. Yield 0·66 g (35%). [^{1}H]NMR δ ppm: 1·13 (6H, dd,

$J = 7$ Hz, $CH(CH_3)_2$), 1·55 (3H, d, $J = 7$ Hz, $CHCH_3$), 2·74 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 5·17 (1H, q, $J = 7$ Hz, $CHCH_3$), 6·73–8·83 (12H, m, aromatic).

2.1.3.9 N-[*2-(3-Chloro-5-trifluoromethylpyridyl)*-N′-(*3-phenoxybenzyloxy)isobutyramidine* (***IV-9***). The title compound was prepared from *N*-[2-(3-chloro-5-trifluoromethylpyridyl)isobutyramide (1·00 g, 3·74 mmol), which was prepared from isobutyryl chloride and 2-amino-3-chloro-5-trifluoromethylpyridine, and **III-1** (0·80 g, 3·72 mmol) according to a method similar to that for compound **IV-3**. The crude product was purified by column chromatography over silica gel using hexane + chloroform (1 + 3 by volume) as eluent, to give a syrup. Yield 0·50 g (29%). [^{1}H]NMR δ ppm: 1·14 (6H, d, $J = 7$ Hz, $CH(CH_3)_2$), 3·92 (1H, m, $J = 7$ Hz, $CH(CH_3)_2$), 5·06 (2H, s, CH_2), 6·85–8·42 (11H, m, aromatic).

2.2 Biological activity

2.2.1 Insecticidal test

The insecticidal activities of compounds were measured against male adult American cockroaches, *Periplaneta americana* L., one to three months old, by the procedure described previously.[21] A methanol solution (1 µl) containing piperonyl butoxide (50 µg) was injected into the abdomen as the synergist to suppress the metabolic mechanism. One hour later, various volumes (1–10 µl) of a methanol solution of each compound were injected into the abdomen of the insects. Three insects were used to test each dose of each compound. Injected insects were kept at 20(±1)°C for 24 h. The minimum dose at which two out of three insects died or became paralyzed was considered as the minimum lethal dose (MLD in moles). Methanol (1–10 µl) with or without the synergist did not affect the MLD value. Measurement of MLD was repeated until values were found to be reproducible. Thus, for each MLD measurement, at least 25 insects were used altogether. The MLD values for test compounds are listed in Table 1. Standard error of the value was ±0·1.

2.2.2 Miticidal tests

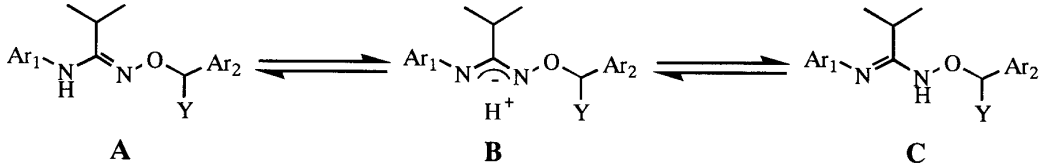
Miticidal activity against three species of house-dust mite, *Dermatophagoides farinae* (the American house-dust mite), *Dermatophagoides pteronyssinus* Trou. (the European house-dust mite) and *Tyrophagus putrescentiae* Schr. (the mold mite), were examined. Each compound was dissolved in acetone to make the concentration 5 or 10 g litre^{-1}. A filter paper (5 × 10 cm) was soaked well in the acetone solution and air-dried. About 150 mites (mixed ages) were released on the filter paper. The miticidal activity was measured after 24 h as the percentage of mites killed. All miticidal tests were done under conditions of 24°C and 75% relative humidity. The miticidal activity values are listed in Table 1.

3 RESULTS AND DISCUSSION

The accurate structure of isobutyramidines **IV** was impossible to elucidate from their NMR spectra. They were obtained as syrups and did not give crystals, so that crystallographic analysis could not be conducted with these compounds. There is a possibility that the C=N double bond exists between the root of the isopropyl side chain and the anilino-nitrogen atom instead of the structure shown in Fig. 1 and Table 1. This isomerization could occur *via* an intermediate anion **B** (Fig. 2) with a prototropy. Because the inductive electron-withdrawing scale of benzyloxy ($\sigma_I = 0{\cdot}43$) is higher than that of substituted phenyl ($\sigma_I = 0{\cdot}15$–$0{\cdot}23$),[22] the 'excess' electron pair in the anion would be attracted toward the alkoxyamino-nitrogen more strongly than toward the anilino-nitrogen. Thus, we supposed the structure of compounds **IV** to be close to that shown in Fig. 1 and Table 1. Moreover, the stereochemistry of the benzylic substituents should be racemic.

The insecticidal activity against the American cockroach by injection did not vary much among compounds **IV** (Table 1). The most active compound **IV-4** was about 20 times more active than the least active compounds **IV-2** and **IV-6**. Except for the second most active compound **IV-1**, the MLD values of the others varied over only a small range. The activity of the most active compound **IV-4** was comparable to that of tetramethrin and much lower than that of phenothrin, by a factor of about 1/60. In contrast to their low insecticidal activity, some compounds such as **IV-1**, **-5**, and **-8** were equally active to or slightly less active than phenothrin and tetramethrin against house-dust mites (Table 1). The activity against the American house-dust mite seems to depend markedly upon the structure, while those against the other two species do not so much.

The structure–activity relationships were not clearly understood for insecticidal as well as miticidal activity because of the limited structural variations. Thus, just 'crude' suggestions and generalizations from Table 1 are as follows.



A **B** **C**

Fig. 2. Isomerism of compounds **IV**.

(1) Compound **IV-4** is somewhat more active than compound **IV-1** insecticidally, because the oxidative metabolism in the insect body at the X_3 position is prevented by the fluorine substitution.[23]
(2) Electron-withdrawing substitution patterns on the anilino-benzene ring are not favorable for insecticidal activity from comparison of the MLD values among compounds **IV-1**, **-5** and **-7**. In compound **IV-1**, the X_1 substituent is electron-donating, whereas the substituent(s) in the other two are electron-withdrawing.
(3) The above descriptions do not apply directly to miticidal activity. The fluorine at X_3 does not show favorable effect on miticidal activity in comparing the indices between compounds **IV-1** and **-4**.
(4) The effect of CH_3 as an electron-donating group is favorable to miticidal activity only when the anilino substituents are strongly electron-withdrawing, as in compound **IV-8**.
(5) A favorable effect of OCH_3, as X_4, is only observed in the miticidal activity of compounds **IV-3** and **-6**.
(6) Variations in the miticidal activity are not exactly parallel among three mite species.

Most often, the substituent introduced at the Y position is CN or C≡CH in pyrethroid insecticides.[24] Because electron-withdrawing Y substituents were thought to make the anilidoxime ether structure unstable to the hydrolysis, we introduced a CH_3 group here. This hypothesis was only valid in compound **IV-8**, the miticidal activity of which is comparable to that of phenothrin. Although further syntheses and structure–activity analyses are required, pyrethroids more hydrophilic than those for agricultural and sanitary uses could be relevant as house-dust miticides. Details of the prediction of lead structures with the software system have been given previously.[15]

REFERENCES

1. Fujimoto, K., Itaya, N., Okuno, Y., Kadota, T. & Yamaguchi, T., A new insecticidal pyrethroid ester. *Agric. Biol. Chem.*, **37** (1973) 2681–2.
2. Ohno, N., Fujimoto, K., Okuno, Y., Mizutani, T., Hirano, M., Itaya, N., Honda, T. & Yoshioka, H., 2-Arylalkanoates, a new group of synthetic pyrethroid esters not containing cyclopropanecarboxylates. *Pestic. Sci.*, **7** (1976) 241–6.
3. Udagawa, T., Numata, S., Oda, K., Shiraishi, S., Kodaka, K. & Nakatani, K., A new type of synthetic pyrethroid insecticide. In *Recent Advances in the Chemistry of Insect Control*, ed. N. F. Janes. Royal Society of Chemistry, London, 1985, pp. 192–204.
4. Sieburth, S. McN., Lin, S. Y., Engel, J. F., Greenblatt, J. A., Burkart, S. E. & Gammon, D. W., Silane analogs of MTI-800: Biology and chemistry. In *Recent Advances in the Chemistry of Insect Control II*, ed. L. Crombie. Royal Society of Chemistry, London, 1990, pp. 142–50.
5. Corbett, J. R., Wright, K. & Baillie, A. C., Insecticides acting elsewhere in the nervous system. In *The Biochemical Mode of Action of Pesticides.* Academic Press, Essex, 1984, 2nd edn, pp. 141–78.
6. Elliott, M., The pyrethroids: early discovery, recent advances and the future. *Pestic. Sci.*, **27** (1989) 337–51.
7. Kato, T., Ueda, K. & Fujimoto, K., New insecticidally active chrysanthemates. *Agric. Biol. Chem.*, **28** (1964) 914–15.
8. Saito, K., Kaneko, H., Tomigahara, Y., Nakatsuka, I. & Yamada, H., Metabolism of imiprothrin isomers in rats: biotransformation and excretion. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **20** (1995) 529–40.
9. Saito, K., Kaneko, K., Tomigahara, Y., Nakatsuka, I. & Yamada, H., Metabolism of imiprothrin isomers in rats: absorption and distribution. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **21** (1996) 49–55.
10. ICI Americas Inc., European Patent Application 317,266, A2, 1989.
11. Bull, M. J., Davies, J. H., Searle, R. J. G. & Henry, A. C., Alkyl aryl ketone oxime *O*-ethers: a novel group of pyrethroids. *Pestic. Sci.*, **11** (1980) 249–56.
12. Matsuda, M., Nakamura, H., Hamada, M., Nishimura, K. & Fujita, T., Quantitative structure–activity studies of pyrethroids. 26. Rates of development of knockdown and depolarizing effects induced by 'kadethric' acid esters and related compounds. *Pestic. Biochem. Physiol.*, **41** (1991) 178–89.
13. Matsuda, K., Oimomi, N., Komai, K. & Nishimura, K., Quantitative structure–activity studies of pyrethroids. 32. Rates of change in membrane potentials of crayfish and cockroach giant axons induced by 'kadethric' acid esters and related compounds. *Pestic. Biochem. Physiol.*, **52** (1995) 201–11.
14. Fujita, T., Nishimura, K., Cheng, Z.-M., Yoshioka, H., Minamite, Y. & Katsuda, Y., EMIL, a system for computer-aided structure transformation of bioactive compounds. In *Natural and Engineered Pest Management Agents, ACS Symposium Series 551*, ed. P. A. Hedin, J. J. Menn and R. M. Hollingworth. American Chemical Society, Washington, DC, 1994, pp. 396–406.
15. Fujita, T., Quantitative structure–activity analysis and database-aided bioisosteric structural transformation procedure as methodologies of agrochemical design. In *Classical and Three-Dimensional QSAR in Agrochemistry, ACS Symposium Series 606*, ed. C. Hansch and T. Fujita. American Chemical Society, Washington, DC, 1995, pp. 13–34.
16. Fujita, T., Adachi, M., Akamatsu, M., Asao, M., Fukami, H., Inoue, Y., Iwataki, I., Kido, M., Koga, H., Kobayashi, T., Kumita, I., Makino, K., Oda, K., Ogino, A., Ohta, M., Sakamoto, F., Sekiya, T., Shimizu, R., Takayama, C., Tada, Y., Ueda, I., Umeda, Y., Yamakawa, M., Yamaura, Y., Yoshioka, H., Yoshida, M., Yoshimoto, M. & Wakabayashi, K., Background and features of EMIL, a system for database-aided bioanalogous structural transformation of bioactive compounds. In *QSAR and Drug Design: New Developments and Applications, Pharmacochemistry Library, Vol. 23*, ed. T. Fujita. Elsevier, Amsterdam, 1995, pp. 235–73.
17. Nishimura, K., Kitahaba, T., Ikemoto, Y. & Fujita, T., Quantitative structure–activity studies of pyrethroids. 14. Physicochemical structural effects of tetramethrin and its related compounds on knockdown activity against house flies. *Pestic. Biochem. Physiol.*, **31** (1988) 155–65.
18. Nishimura, K., Kobayashi, T. & Fujita, T., Quantitative structure–activity studies of pyrethroids. 23. Rate of

decrease in sodium tail currents induced by substituted benzyl chrysanthemates and pyrethrates in crayfish giant axons. *Pestic. Biochem. Physiol.*, **40** (1991) 99–110.
19. Fujii, T., Wu, C. C. & Yamada, S., Preparation and nuclear magnetic resonance spectra of alkoxyamines. *Chem. Pharm. Bull.*, **15** (1967) 345–9.
20. Mandel, G. & Hill, A. J., The conversion of formamides into formamidines. *J. Amer. Chem. Soc.*, **76** (1954) 3978–82.
21. Nishimura, K., Okimoto, H., Ueno, T., Shiraishi, S., Kodaka, K. & Tomoda, K., Comparison of acaricidal, insecticidal and nerve activities of halfenprox (MTI-732) and related compounds. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **21** (1996) 311–16.
22. Charton, M., Electrical effect substituent constants for correlation analysis. *Prog. Phys. Org. Chem.*, **13** (1981) 119–251.
23. Fuchs, R. A., Hammann, I., Behrenz, W. & Stendel, W., DT Patents 2,709,264, 1978.
24. Henrick, C. A., Anderson, R. J., Carney, R. L., Garcia, B. A. & Staal, G. B., Some aspects of structure–activity relationships in pyrethroids. In *Recent Advances in the Chemistry of Insect Control*, ed. N. F. Janes. Royal Society of Chemistry, London, 1985, pp. 133–61.